REMARKS

I. STATUS OF CLAIMS

With entry of this amendment, claims 1-6, 9-37, 39-42, and 44-77 are pending; claims 1, 2, 9, 11,13, 30, 39-42, 44, and 65 are amended and claims 7, 8, 38, and 43 are canceled without prejudice and/or disclaimer. Amendments to claims 1, 30, and 65 are supported by original claims 7, 8, and 43. Amendments to the remaining claims are made to clarify subject matter described therein and are supported by the claims themselves and/or the present specification. As such, no new matter is added by these amendments.

II. OBJECTION UNDER 37 C.F.R. § 1.75(c)

The Office objects to claims 38-51 under 37 C.F.R. § 1.75(c) as being in improper dependent form, i.e., failing to further limit the subject matter of the previous claim. Office Action at page 2. In particular, the Office contends that "[c]laims 38-51 recite an intended use without reciting a specific chemical or physical property of the formulation of claim 30 from which they depend." *Id.* In order to advance prosecution, Applicant has amended and/or canceled select subject matter in claims 38-51.

By incorporating the subject matter of claims 38 and 43 into independent claim 30, the subsequent dependent claims, i.e., claims 37-42 and 44-51, further limit the subject matter of the respective previous claims. Accordingly, the objections raised to claims 38-51 are now moot with the entry of the amendments provided herein.

III. REJECTIONS UNDER 35 U.S.C. § 112

A. FIRST PARAGRAPH

The Office rejects claims 1-29 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Office Action at page 2. The Office asserts that Applicant fails to convey possession of the invention because "there are no working examples . . ., wherein any outcome is noted." *Id.* at page 5. In addition, the Office finds that "[i]n Example 1, page 74 of the specification, a hypothetical situation is described ... on pages 82-83 of the specification in Example 7, another hypothetical situation is described ..." for which there are no conclusions with respect to minimizing at least one side effect associated with the administration of a conventional formulation or reducing gastrointestinal motility in a subject caused by the pathological condition. *Id.* As a result, the Office concludes a skilled artisan would require a more detailed description of the disease states and the minimization of side effects. *Id.* The Office further emphasizes that there are no working examples that meet all the claim limitations thereof. *Id.* Applicant respectfully disagrees and traverses the rejection for at least the following reasons.

The Office focuses this Section 112, first paragraph, rejection on the lack of working examples, i.e., "there are no working examples." Office Action at page 5, ll. 2-4, 19, and 20. The presence or absence of a working example, however, is not the standard by which compliance with Section 112, first paragraph is judged. All that is required is that the specification reasonably convey to one of ordinary skill in the art that as of the filing date of the application, applicant was in possession of the present

invention; how the specification shows possession is immaterial. *See In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983). Thus, Applicant's use of hypothetical examples does not evidence a lack of written description.

Moreover, "the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1978). The Office's explanation that there are no conclusions from these examples showing minimization of side effects and/or reduce gastrointestinal motility does not even come close to discharging the burden on the Office to establish that the application, as originally filed, inadequately describes the subject matter in question by not giving particular examples. After all, the specification is directed to a person of ordinary skill in the art. The Office furthermore has failed to establish that one of ordinary skill in the art would have found that Applicant was not in possession of the subject matter recited in the present claims based on the breadth thereof and mere allegations of hypothetical exemplification. Accordingly, a *prima facie* case for lack of written description has not been established and Applicant respectfully requests the withdrawal of the rejection.

B. SECOND PARAGRAPH

The Office rejects claim 2 under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the Markush language. Office Action at page 2. The Office suggests that the word "and" be inserted before the term "spastic colon." *Id.* Based on the amendment contained herein, Applicant amended claim 2 to include the word "and"

before "spastic colon." Based on this amendment, the rejection is moot and Applicant respectfully requests its withdrawal.

IV. REJECTION UNDER 35 U.S.C. § 103

The Office further rejects claims 1-77 under 35 U.S.C. § 103(a) as unpatentable over WO 00/35280 to Shytle et al. or WO 00/35279 to Shytle et al. (since both references are related and share a common disclosure, reference herein to "Shytle" encompasses both of the two references). Office Action at page 6. According to the Office, Shytle teaches the administration of mecamylamine for the treatment of gastrointestinal motility disorders. *Id.* Although not expressly disclosed in Shytle, the selection of an optimal dosage form, dosages, regimens, optimal isomers, multiple drug therapy, and testing using a U.S. Pharmacopoeia (USP) Type 2 apparatus would be all within the purview of those skilled in the art of formulation chemistry. *Id.* As such, the Office concludes that claims 1-77 are obvious. Applicant respectfully disagrees and traverses the rejection for at least the following reasons.

Shytle recognizes that despite mecamylamine's proven efficacy in the treatment of hypertension, the side effects associated with mecamylamine treatment lead to its "demise as a first line treatment for essential hypertension." Shytle at page 1. For example, the generalized ganglionic blockade results in atony of the bladder and gastrointestinal tract, impaired sexual function, cycloplegia, xerostomic, diminished perspiration, and postural hypotension. *Id.* According to Shytle, better symptom control and fewer side effects are needed for mecamylamine treatment. *Id.* at page 6. To answer such a need, Shylte provides a composition that includes a therapeutically

effective amount of exo-R-mecamylamine or a pharmaceutically acceptable salt thereof, *substantially free of exo-S-mecamylamine* in combination with a pharmaceutically acceptable carrier. Shytle at Abstract, 7, and 20-22.

Shytle, moreover, teaches that "it is generally observed that, by administering an effective amount of *only exo-R-mecamylamine*, it is possible to accomplish a more 'targeted' therapy, which provides the desired effect without the consequences of all the other pharmacological effects." *Id.* at page 8 (emphasis added). To do so, Shytle formulates exo-R-mecamylamine in pharmaceutical compositions known in the art with traditional doses. *Id.* at page 12. Accordingly, Shytle teaches that by using a particular isomer of mecamylamine (i.e., R-mecamylamine) one can achieve better symptom control with fewer side effects. Although the present invention encompasses mecamylamine as in Shytle, its' teachings are in a different direction and take treatment with and compositions comprising mecamylamine a step further.

As provided in amended independent claims 1, 30 and 65 (from which all claims depend), the present invention is directed to methods and compositions reducing gastrointestinal motility comprising administering a gastrointestinal reducing amount of N-2,2,3-tetramethylbicyclo-[2.1.1]heptan-2-amine, or a pharmaceutically acceptable salt thereof, wherein the N-2,2,3-tetramethylbicyclo-[2.1.1]heptan-2-amine is administered in the form of a modified-release formulation, and produces a peak:trough plasma ratio of less than about 4:1. Instead of using a particular isomer to produce a "targeted" therapy, as in Shytle, the present invention uses a modified release composition that

produces a peak:trough ratio of less than 4:1 of N-2,2,3-tetramethylbicyclo-[2.1.1]heptan-2-amine, or a pharmaceutically acceptable salt thereof.

In order to establish a *prima facie* case of obviousness, three requirements must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143 (8th ed. Rev. 3, 2005). Based on the amended claims, Shytle fails to teach all the claim limitations. Namely, Shytle fails to teach a modified-release formulation having the peak:trough plasma ratio as recited in the present claims.

In Shytle, the exo-R-mecamylamine compositions are taught as being "formulated by procedures known in the art so as to provide, rapid, sustained, or delayed release of any or all of the compounds after administration. In addition, to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and/or delivery devices . . . ." Shytle at pages 12, 13. But this is not enough to render obvious a particular peak:trough plasma ratio. Shytle's teachings merely suggest that *any* formulation will work. It is unclear how one of ordinary skill in the art would use such a broad teaching to arrive at the presently claimed invention without any guidance. Shytle provides no teachings or suggestions to do so. Moreover, Shytle discloses many formulations that necessarily

fall outside the scope of the present invention and thus, Shytle's teachings fail to necessarily teach the present invention.

Even the Office's argument that "the selection of optimal dosage forms, dosages, dosage regimens and an optional isomer, or the racemic mixture, are parameters *well within the purview of those skilled in the art* of formulation chemistry through no more than routine experimentation" fails. Office Action at page 6 (emphasis added). Just because a modification of the prior art would be within the ordinary skill of the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to do so. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1365, 55 U.S.P.Q.2d 1313, 1318 (Fed. Cir. 2000) (reversing an obviousness rejection involving technologically simple concept because there was no finding as to the principle or specifics understanding within the knowledge of a skilled artisan to make the claimed invention); *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999) (explaining that the level of skill in the art cannot be relied upon to provide the suggestion to combine references).

Accordingly, for at least the above-mentioned reasons, Shytle fails to establish a *prima facie* case of obviousness of any of the pending claims and thus, Applicant respectfully requests the withdrawal of the rejection.

V. CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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